

EDQM Conference

The European Pharmacopoeia Is it prepared for the future?

Workshop 5

14-15 October 2010
Prague, Czech Republic



©2010 EDQM, Council of Europe, All rights reserved



Workshop 5

 Dr Jean-Louis Robert

 Mr Mark Wiggins

 Dr Bernhard Wolf

 Dr Philippe Girard



©2010 EDQM, Council of Europe, All rights reserved



Quality of Medicines in a globalised World The European Pharmacopoeia Is it prepared for the Future?

Dr. Jean-Louis ROBERT
Chair CHMP/CVMP Quality Working Party
Laboratoire National de Santé
Luxembourg

1

Objectives of Pharmacopoeias

- Aim of Pharmacopoeias
Harmonisation of requirements in the field of medicinal products within a region (political unit or international organisation)
- Historically:
 - 1871: Deutsches Reich
 - 1872: Pharmacopoeia Germanica, edition 1
 - 1963: First discussion EC about free circulation of medicinal product
 - 1964: European Pharmacopoeia
 - 1965: First EC directive 65/65
- 1948: International Pharmacopoeia, WHO
- 1990: ICH – PDG process

2

European Pharmacopoeia and Quality of Medicines

- 30-40 years ago: main requirements for MA application described in Pharmacopoeias
- Set of mandatory requirements (standards), described in
 - General monographs
 - General chapters
 - Specific monographs: mostly APIs, but also vaccines
- Advantages e.g.:
 - Regulators:
 - Important tool during assessment
 - OMCL: marketing control
 - Industry:
 - Predictable requirements
 - Collaboration Regulators - Industry

3

European Pharmacopoeia and challenges (1)

- Globalisation – multi source materials
 - Different impurity profiles
 - Transparency of monographs
 - Certification of suitability process
- ICH – process: new paradigm in pharmaceutical quality:
 - More emphasis on manufacturing process, more knowledge about material attributes,
 - Functionality testing
 - RTRT versus end product testing
 - RTRT and sample size e.g. UDU
 - Impurities controlled at an intermediate stage rather at final product (how to make in line two different manufacturing processes)

4

European Pharmacopoeia and challenges (2)

- Introduction of new technology: Raman, NIRS, Acoustics,
- Counterfeiting
- Revision of monographs to make them in line with new scientific progress
 - HPLC versus fast LC
 -
- To cope with new guidelines (CHMP)
 - Residual metals/solvents

5

European Pharmacopoeia and challenges (3)

- What is the future in pharmaceuticals?
 - Cell therapy
 - Gene therapy
 - Nanotechnology and associated technology
 - E.g. Transmission electron microscopy
 - Personalized medicines?

6

European Pharmacopoeia: Prepared for the future?

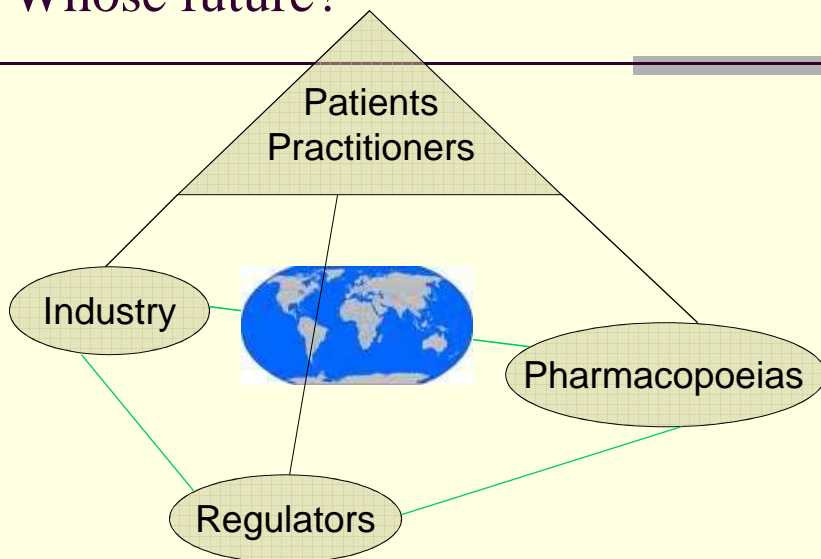
- Elements are so far in place: they need to be used appropriately (see also General Notices).
- Flexibility/adaptation requested without decrease in quality.
 - Ph. Eur. remaining the reference
- Close collaboration between European Pharmacopoeia and Competent Authorities and including Industry.
- Harmonisation of Pharmacopoeias

The European Pharmacopoeia – Is it Prepared for the Future?

EDQM Conference – Prague
14-15 October 2010

J. Mark Wiggins
Compendial Affairs
Merck/MSD

Whose future?



Shared Goals / Challenges

- To provide safe, effective, high-quality medicines to patients in an increasingly global environment.

- “The Need for International Harmonisation – Globalisation and expansion in international trade present a growing need to develop global quality standards for medicines... (these) standards are a vital instrument for registration, market surveillance, and free movement and trade of medicines among as many countries as possible...”
<http://www.edqm.eu/site/International-Harmonisation-614.html>

Ideal Pharmacopoeia* (1)

- The "Ideal Pharmacopoeia" would:
 - provide appropriate standardisation
 - to facilitate drug registration
 - and support regulatory agencies
 - through a single, global compendial standard.

*

J. Mark Wiggins, et. al. (PhRMA Compendial Liaison Team),
Pharmaceutical Technology, Vol. 32, No. 11, pp. 122-125 (November 2008)

Ideal Pharmacopoeia (2)

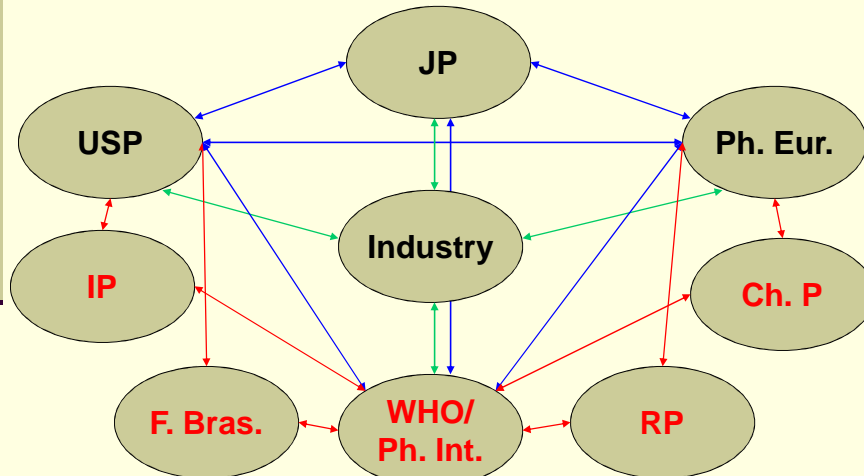
- Single, Global Compendial Standard
 - Ph. Eur. 6.0 Conference – Revelation
 - Harmonisation
 - PDG – ICH Q4B
 - Ph. Eur., USP, JP
 - Brasil, Russia, India, China, etc.
 - Ph. Int. – WHO
 - Prospective Harmonisation
 - Mutual Acceptance
 - Legislative Revision

Ideal Pharmacopoeia (3)

- PDG – ICH Q4B: Retrospective Harmonisation
 - General Chapters
 - Excipient Monographs
 - Gaps:
 - API / Product Monographs
 - “X”P (Non-PDG / Non-ICH Pharmacopoeias)
- Prospective Harmonisation Pilot Program
 - API Monographs
 - Ph. Eur. / USP
 - Gaps:
 - Product Monographs
 - JP / “X”P

Global Compendial Standards

Future Collaboration?



Ideal Pharmacopoeia (4)

- Provide appropriate standardisation
- Facilitate drug registration
 - General Notices
 - General Chapters
 - Ingredients
 - Excipients
 - Drug Substance
 - Products (Dosage Forms)
 - Pharmaceuticals
 - Vaccines
 - Therapeutic Proteins

Ideal Pharmacopoeia (5)

- Supports regulatory agencies
 - Needs and objectives aligned:
To provide safe, effective, high-quality medicines to patients in an increasingly global environment.
 - Glycerin / Heparin / Melamine
 - Residual Solvents
 - Metal Impurities
 - Related Substances
 - Uniformity of Dosage Units
 - Dissolution Calibration

Monographs / Reference Standards (1)

Practical Matters / Details

- Timing of Monograph Submissions
- Assay – APIs
 - Titration vs. HPLC
 - Certified Reference Materials
 - Interchangeability of Reference Standards
- Impurities / Related Substances (ICH Q3A, Q3B)
 - Quantitation vs. Limit Test
 - Impurities vs. Degradates (Product Monographs)
 - Impurity Reference Standards
- Metal Impurities (ICH Q3D)
 - Heavy Metals Test vs. ICP-MS/OES

Monographs / Reference Standards (2)

Practical Matters / Details

- ICH Q8, Q9, Q10 / QbD / PAT
 - QbD in manufacturing (UDU, NIR)
 - QbD in analytical methods

Pharmaceutical Technology, Vol. 34, No. 2, pp. 52-59 (February 2010)
- Functionality-Related Characteristics – Excipients
- Acceptable, Equivalent, or Better (USP)
- Performance-Based Monographs (USP)
- Flexible Monographs (USP)
- Pending Standards (USP)
- Contamination / Adulteration / Counterfeiting
- Other considerations?

Is Ph. Eur. Prepared for the Future?

- Yes...
 - Already international
 - Effective collaborations
 - EC Pharmacopoeias / Observers
 - EU Regulators / OMCLs
 - Industry
- Continue focus on harmonisation
- Expand with WHO – Ph. Int.
- Expand with Ch. P, IP, RP, F. Bras., etc.
- Focus on details, e.g. impurity limits



Thank you

I look forward to the discussion...

The European Pharmacopoeia - Is it prepared for the future?

A Statement by the Pharmaceutical Industry

Dr. Bernhard Wolf
Merckle GmbH
A member of the ratiopharm group

Quality deficiencies

A long list of major quality deficiencies

- **Gentamycin (CN)**
- **Heparin (CN)**
- **Clopidogrel (IN)**
- **Loperamid (IN)**
- **Oxytetracyclin (CN)**
- **etc.**

The heparin case

ratiopharm

- **End of 2007 - January /February 2008**
US-case reports on
hypotension, allergic reactions and even death after heparin administration
- **February 2008**
FDA Alert on heparin from chinese origin
- **March 2008**
similar case reports in Germany
- **Identification of OSCS as source of ADR (?)**
(Kishimoto et al N.Engl.J.Med April 2008)
- **Publication of NMR- and CE-methods**

The heparin case

ratiopharm

- **August 2008:**
Revised Monograph in Ph.Eur., rapid implementation
Additional requirements:
 - Nuclear magnetic resonance spectrometry ... **specifications approved by the competent authority**
 - Capillary electrophoresis
- **August 2010:**
Revised Monograph in Ph.Eur., rapid implementation
Identification: NMR and SAX-HPLC
Related substances:
 - Chondroitin- + Dermatansulfate: $\leq 2.0\%$
 - any other impurity: no other peak than CS and DSPotency: ≥ 180 IU / mg

Potential for Improvements

- **Monographs**
- **Certificates of Suitability**
- **Reference substances**

Monographs

- **Monographs should be updated periodically to represent and ascertain the available quality on the market (e.g. penicillins).**
- **To fix acceptable and realistic limits in monographs the cooperation of manufacturers, licensing authorities, and EDQM Certification Unit is needed.**
- **Harmonisation efforts of monographs and General Chapters with USP and JP should be intensified.**

Monographs

ratiopharm

- **Wording has to be unequivocally understandable for users (other impurities, any other impurity, specified impurities etc.).**
- **Include in the preamble of a monograph if a transition period for implementation is allowed (e.g. 2.9.40 Uniformity of dosage units).**
- **Indicate which impurities are degradation or by products. The latter do not have to be considered in the finished pharmaceutical products.**

Monographs

ratiopharm

- **Typical chromatograms using different brands of columns should be available on the knowledge database and not only in Pharmeuropa.**

Certificates of Suitability

ratiopharm

- The initiative to make GMP-inspections before granting a CEP should not only be limited to sterile APIs (without excluding the responsibility of the pharmaceutical companies for their products).
- Implement more transparency by publishing inspected companies and major deficiencies.

Reference substances

ratiopharm



- Since the allocation of impurities is often problematic peak-identification mixtures in conjunction with sample chromatograms would be preferable.
- Impurities listed in the transparency list which are not specified are not available as CRS. Allocation of these impurities in sample chromatograms should be published in the knowledge data base.
- CRS should be available before a new monograph comes into force to be able to implement the methods in the labs.

**Thank you
for your time and attention !**




Official Medicines Control Laboratory

- Part of Swissmedic
- Experimental control of the quality of medicines
 - Market surveillance
 - Authorization
 - Pharmacopoeia (Helv. and Eur.)
 - Official batch release (OCABR)
 - Other sectors of Swissmedic (legal)
 - Third parties (states, justice)
 - > 40 Collaborators
- > 1500 m² of laboratory
- > 250 analytical devices
- > 3000 mandates and reports/releases
- Accreditation ISO 17'025


SWISSmedic

3




What we appreciate...

- A set of rules defining a legally binding standard of quality
- Robust and validated methods
- SST
- Suitable reference materials
- Definition of the range of validity of the method (2.2.46), certain flexibility
- A knowledge database in case of difficulties
- Possibility to get advice (*i.e.* FAQ and EDQM HelpDesk)
- P4 procedure
- Adoption by consensus



SWISSmedic


4



Challenges

- **Detailed method descriptions**
 - Freedom of the users versus foolproof methods
 - Generic versus brands (*i.e.* specific columns)
 - One method for all manufacturers
- **Integration of technical improvements**
 - UHPLC
 - Methods relying on chemometrics (*e.g.* RAMAN)
 - State of the art methods (*e.g.* 254 nm, antibiotics)
- **Fast integration of regulatory needs (reaction time)**
 - Genotoxic impurities
 - Substandard, counterfeit, fraud API (*e.g.* Heparin)


SWISSmedic 5



What we would like to have...

- **Monographs for finished products**
 - Frequent in national pharmacopeias
 - Effort versus benefit
 - Generic testing
 - Reduction of hurdles for MA
- **Reference materials**
 - Uncertainties of assigned values (CRS)
 - Calculation of measurement errors
 - More impurities, purity of impurities...
- **Faster adaptation of changes (technical and regulatory)**
- **Equivalents to regulatory frameworks (*e.g.* equivalent to ICH Q3B)**

SWISSmedic 6





What we would like to avoid...


One Method Pharmacopoeia

- 'Analyze a suitable sample with an adequate method using qualified equipment in order to generate compliant results'
- OMCL with access to the methods of the MAH...
- ...but why do we need an pharmacopoeia ?
- ...users don't all have access to methods...

• **Excessive costs to obtain standards and the Pharmacopoeia**




 7



Ph. Eur. prepared for the Future?

Yes !

(... **but** ...with some revisions,
a little improvement and continuous evolution)

 8